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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,586	12/12/2005	Gabriele Multhoff	KNAUTHE-09734	3810

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,586	MULTHOFF, GABRIELE	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments/Arguments

Applicant's amendments and arguments filed June 8, 2007 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn. As amended, the invention is substantively distinct from the previously presented claims, requiring now active administration to a patient in need thereof, where before the claims required no active administration *per se*, and thus the previous rejections are withdrawn as moot. New grounds of rejection are necessitated by the amendments and are presented below.

Claim Objections

Claim 17 is objected to because of the following informalities: The grammar of claim 17 should be amended to more clearly reflect the claim is drawn to "A method of treating". Additionally, it appears that the article "a" is missing before "tumor". Further, Applicant is suggested to reorder the claim such that 'tumor' is the last member of the Markush group. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites, "wherein said tumor cells or cells affected by said infection...", however the claim lacks clear antecedent basis for 'said tumor cells or cells affected by...', as the claim preamble makes no reference to 'cells'.

Claims 25-27 recite that the granzyme B is administered in "a final concentration of...", however it is unclear whether the concentration is the concentration of the composition administered or the concentration achieved *in vivo* after administration, and thus the claims are vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by TROUET (WO 01/91798 A1).

The instant claims are drawn generally to administration of granzyme B to a human to treat tumor, viral or bacterial infection or inflammatory diseases.

Trouet teaches granzyme B induces apoptosis(e.g. page 31) and is conjugated to a delivery peptide as a "tumor specific prodrug formulation" (e.g. Example 14, page 53), further teaching pharmaceutical compositions (e.g. claim 56) and the method of inhibiting tumor growth *in vivo*, *ex vivo* or *in vitro* with the prodrugs of Trouet (e.g. claim 53). Trouet teaches how one would determine effective dosages for practicing the methods (e.g. Page 39, *5.9.2 Effective Dosages*).

Here, Trouet does not distinguish the type of tumor cell, and thus embraces all tumor cells, including those expressing Hsp70 on the surface. Furthermore, nothing in Trouet

precludes administration to cells expressing Hsp70. Additionally, the limitations of steps (b) and (c) are *in vivo* and cannot be controlled by the administration of the drug, and thus would inherently occur when granzyme B is administered as in the method of Trouet. Further, it is noted that claim 28 does not require selection of 'viral infection', and merely limits the Markush group to a subset (e.g. claim 17 is A, B or C, claim 28 is A, B' or C), and thus properly is rejected as reading upon tumor.

With regards Trouet teaching a prodrug form, the instant claim does not exclude such prodrug forms, as the instant claims requires administration of a pharmaceutically effective amount of granzyme B and administration of the prodrug form of Trouet delivers a pharmaceutically effective amount of granzyme B. Here, the prodrug form is merely considered a means to deliver the peptide to the cell and does not materially change the fact that it delivers a pharmaceutically effective amount of granzyme B, particularly since the claims do not require a specific form of granzyme B be administered, e.g. i.v. solution consisting of granzyme B and a carrier.

Claims 17 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by TROUET (II) (Previously cited as US 2004/0014652 A1; PTO-892, 3/6/07). Trouet (II) is the National Stage Application of Trouet, *supra*.

The instant claims are presented *supra*.

Trouet (II) teach Granzyme B as an agent for treatment of tumors and cancers (paragraphs [0013], [0139], [0140-0141], and [0277-0281]) and claim Granzyme B as an agent in compositions for treating cancer cells in claims 29, 35, and 51. Trouet (II) discloses the addition of a masking or protecting moiety to Granzyme B, among other agents of interest, in order to give it more protection from proteases and peptidases present in the circulatory system as well as allowing it to penetrate the nuclear membrane more readily once it is in the cell. Trouet teaches that therapeutically effective and safely tolerated amounts of the compositions should be used (paragraph [0189]), and do broadly teach how to use findings from cell culture and animal studies to determine safe and effective doses and dosing schedules suitable to the organism, disease and agent being used (e.g. paragraph [0184] and [0205]).

Here, Trouet does not distinguish the type of tumor cell, and thus embraces all tumor cells, including those expressing Hsp70 on the surface. Furthermore, nothing in Trouet precludes administration to cells expressing Hsp70. Additionally, the limitations of steps (b) and (c) are *in vivo* and cannot be controlled by the administration of the drug, and thus would inherently occur when granzyme B is administered as in the method of Trouet. Further, it is noted that claim 28 does not require selection of 'viral infection', and merely limits the Markush group to a subset (e.g. claim 17 is A, B or C, claim 28 is A, B' or C), and thus properly is rejected as reading upon tumor.

With regards Trouet teaching a prodrug form, the instant claim does not exclude such prodrug forms, as the instant claims requires administration of a pharmaceutically effective amount of granzyme B and administration of the prodrug form of Trouet delivers a pharmaceutically effective amount of granzyme B. Here, the prodrug form is merely considered

a means to deliver the peptide to the cell and does not materially change the fact that it delivers a pharmaceutically effective amount of granzyme B, particularly since the claims do not require a specific form of granzyme B be administered, e.g. i.v. solution consisting of granzyme B and a carrier.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over TROUET or TROUET (II). Trouet and Trouet (II) are discussed together as they have the same disclosure and teachings.

The instant claims and teachings of Trouet and Trouet (II) are presented *supra*. The instant claims are further drawn to the granzyme B being adminsiterd at various final concentrations, e.g. about 6 ng/ml.

Trouet and Trouet (II) each teach administration of granzyme B to treat/inhibit growth of tumors and means by which one could determine the effective dosages to administer, as discussed above.

Trouet and Trouet (II) are each relied upon for the reasons discussed above. If not expressly taught, based upon the overall beneficial teaching provided by this reference with respect to making dosages and determination of the effective dosages, in the manner disclosed therein, the adjustments of particular conventional working conditions (e.g., determining one or more suitable dosage ranges of granzyme B to administer), is deemed merely a matter of judicious selection and routine optimization, as it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. final concentration of granzyme B adminsitered), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05), and such selection and optimization is well within the purview of the skilled artisan.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Art of Record

Art pertinent to the claimed invention, but not relied upon above is identified on the enclosed PTO-892.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andrew D Kosar
Patent Examiner
Art Unit 1654